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## **Guidelines for the diagnosis and management of methylmalonic acidaemia and propionic acidaemia: First revision**

Forny, Patrick ; Hörster, Friederike ; Ballhausen, Diana ; Chakrapani, Anupam ; et al ; Huemer, Martina ; Baumgartner, Matthias R

**Abstract:** Isolated methylmalonic acidaemia (MMA) and propionic acidaemia (PA) are rare inherited metabolic diseases. Six years ago, a detailed evaluation of the available evidence on diagnosis and management of these disorders has been published for the first time. The article received considerable attention, illustrating the importance of an expert panel to evaluate and compile recommendations to guide rare disease patient care. Since that time, a growing body of evidence on transplant outcomes in MMA and PA patients and use of precursor free amino acid mixtures allows for updates of the guidelines. In this article, we aim to incorporate this newly published knowledge and provide a revised version of the guidelines. The analysis was performed by a panel of multidisciplinary health care experts, who followed an updated guideline development methodology (GRADE). Hence, the full body of evidence up until autumn 2019 was re-evaluated, analysed and graded. As a result, 21 updated recommendations were compiled in a more concise paper with a focus on the existing evidence to enable well-informed decisions in the context of MMA and PA patient care.

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## ORIGINAL ARTICLE



WILEY

# Guidelines for the diagnosis and management of methylmalonic acidaemia and propionic acidaemia: First revision

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## Abstract

Isolated methylmalonic acidaemia (MMA) and propionic acidaemia (PA) are rare inherited metabolic diseases. Six years ago, a detailed evaluation of the

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available evidence on diagnosis and management of these disorders has been published for the first time. The article received considerable attention, illustrating the importance of an expert panel to evaluate and compile recommendations to guide rare disease patient care. Since that time, a growing body of evidence on transplant outcomes in MMA and PA patients and use of precursor free amino acid mixtures allows for updates of the guidelines. In this article, we aim to incorporate this newly published knowledge and provide a revised version of the guidelines. The analysis was performed by a panel of multidisciplinary health care experts, who followed an updated guideline development methodology (GRADE). Hence, the full body of evidence up until autumn 2019 was re-evaluated, analysed and graded. As a result, 21 updated recommendations were compiled in a more concise paper with a focus on the existing evidence to enable well-informed decisions in the context of MMA and PA patient care.

### KEYWORDS

diagnosis and management, guidelines, inherited metabolic disease, methylmalonic acidemia, propionic acidemia

## 1 | INTRODUCTION

The first guidelines on isolated methylmalonic acidemia (MMA) and propionic acidemia (PA) were published in September 2014 and accessed over 53 000 times on the journal's website and cited 182 times according to Web of Science (July 2020).<sup>1</sup> The attention the guidelines received signifies the interest and utilisation by health care professionals of this evidence evaluation and deduced recommendations as provided by an expert panel. Especially in the rare disease field, structured evaluation of the present evidence is of great value, as the process involves specific considerations related to the rarity of these types of disorders. High-quality trials in large samples which would produce firm and reliable evidence are scarce given the small patient populations, often rendering the present evidence low quality. As a result, evidence collected from case series or smaller studies needs to be carefully evaluated.

The advances in the field and the success of the first MMA/PA guidelines prompted us to provide an update 6 years later. The guidelines presented here use a different and more up-to-date system to evaluate evidence than the first version, the 'Grading of Recommendations, Assessment, Development and Evaluation' (GRADE) approach,<sup>2</sup> which is more suitable for the rare disease field, as it partially accounts for the above described challenges. Due to the change of methods, the whole body of literature on MMA and PA referenced on PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) was newly evaluated.

### Synopsis

Structured evidence evaluation of the present literature resulted in 21 recommendations on how to diagnose and manage patients with methylmalonic acidemia and propionic acidemia.

Since the publication of the initial guidelines, new advances have been made, and more data have been published on MMA and PA. For example, more patients have been organ transplanted and their outcomes were published. Several novel studies investigated the impact of using precursor free amino acids (PFAAs) as part of the dietary regimen of MMA and PA patients. The updated guidelines presented here aim to include this new data, while at the same time attempt to streamline and summarise sections for which the evidence has not significantly changed. The reader is provided with the full recommendations for MMA and PA diagnosis and management but is referred to the initial guidelines for more details regarding certain aspects.

This first revision of the MMA and PA guidelines covers the same subtypes of isolated MMA and PA as before. MMA is caused by a deficiency of the methylmalonyl-CoA mutase enzyme (MMUT), either by a direct defect of the enzyme, or by a deficient synthesis of its cofactor adenosylcobalamin. Precursors of this pathway are derived from specific amino acids (valine,

isoleucine, threonine, methionine), propionate produced by gut bacteria and odd chain fatty acids as well as the cholesterol side chain (Figure 1). Under isolated MMA, the following gene defects are included: deficiencies of *MMUT* (OMIM #251000), *MMAA* (OMIM #251100), *MMAB* (OMIM #251110) and truncating mutations towards the N-terminal in the *MMADHC* gene (OMIM #277410).<sup>3</sup> PA (OMIM #606054) is caused by mutations in the *PCCA* (OMIM #232000) or *PCCB* gene (OMIM #232050), resulting in deficiency of the propionyl-CoA carboxylase enzyme function.<sup>4</sup>

## 2 | METHODOLOGY AND OBJECTIVES

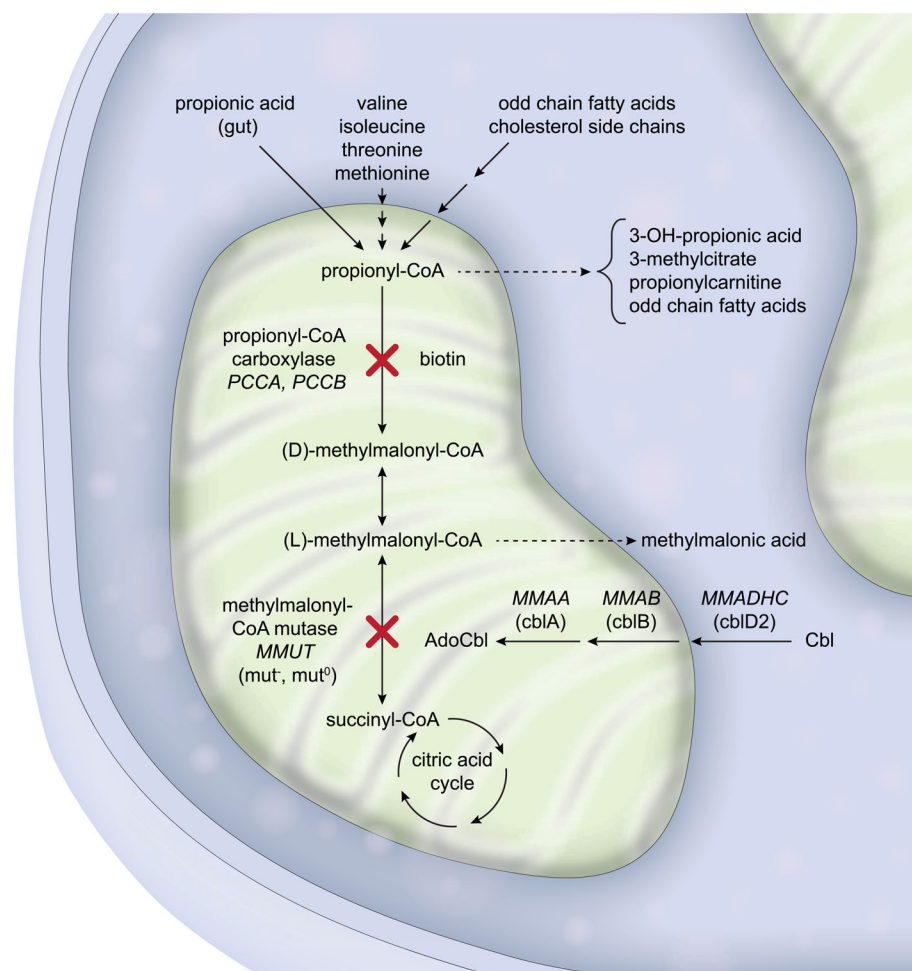
The presented revision of the guidelines for MMA and PA was undertaken by a panel of 21 health care professionals who work in the field of metabolic medicine. P. F. (secretary), M. R. B., F. H. (co-chairs) and M. Huemer (methodology and moderation) formed a core panellist group to coordinate organisational and content aspects. The panel further included paediatric metabolic

specialists (D. B., A. C., K. A. C., C. D.-V., S. C. G., S. G., T. H., D. K., S. S.-B., G. T., M. W.), a metabolic adult physician (M. Hochuli), a paediatric metabolic dietitian (M. D.), paediatric neurologists (G. H., D. M.), a medical doctor in training and PhD student in inherited metabolic diseases (F. M.) and a clinical biochemist (J. O. S.). The panel was supported by external reviewers for review of nephrology, cardiology, neurology and dietetic recommendations and two patient representatives. The panel met in person in September 2019 and November 2019).

### 2.1 | Literature search and evidence grading

In the initial guidelines, the method to collect the evidence was based on SIGN.<sup>5</sup> In the revised guidelines, the GRADE methodology was used.

To gather the initial evidence base, a PubMed search was performed on September 29, 2019 with the following search term: ("propionic acidemia" OR "propionic acidemia" OR "propionic aciduria" OR "methylmalonic acidemia" OR "methylmalonic acidemia" OR "methylmalonic aciduria")



**FIGURE 1** Propionyl-CoA is metabolised in the mitochondria by specific enzymes. Defects in the genes *MMUT*, *MMAA*, *MMAB* or *MMADHC* (more specifically variant 2) lead to isolated MMA, whereas defects in *PCCA* or *PCCB* lead to PA. Propionyl-CoA is derived from various sources and is metabolised to alternative products in the case of accumulation in the above-described defects. In addition, accumulating methylmalonyl-CoA in isolated MMA is hydrolysed to methylmalonic acid, the main biomarker of this disease. Gene names are italicised, complementation groups are in parenthesis. MMA, methylmalonic acidemia; PA, propionic acidemia

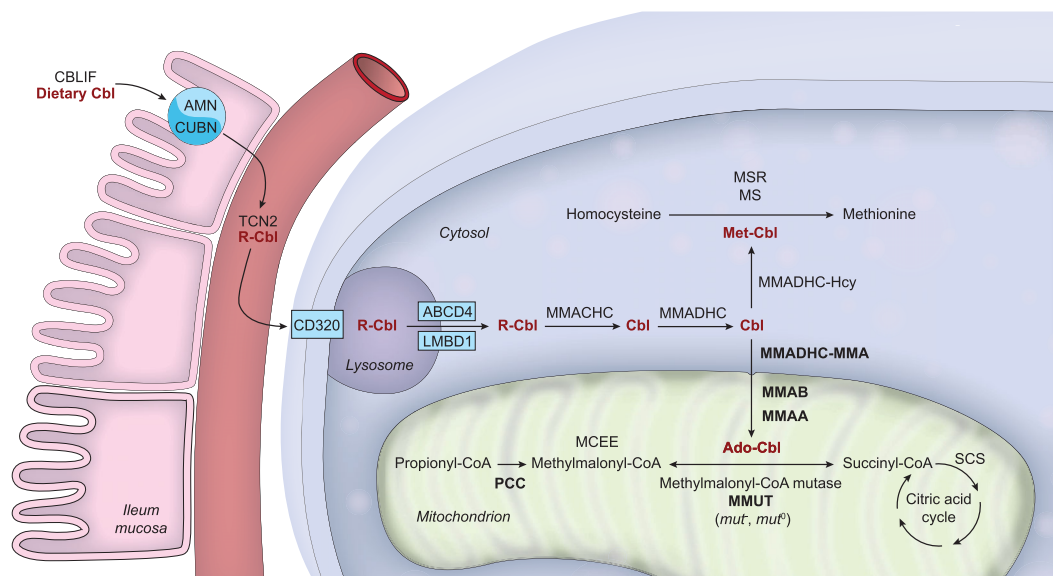
OR “propionic acidemias” OR “propionic acidaemias” OR “propionic acidurias” OR “methylmalonic acidemias” OR “methylmalonic acidaemias” OR “methylmalonic acidurias”) AND (“1900/01/01”[Date - Publication]: “2019/09/05”[Date - Publication]) AND (english[Language]) NOT (animals[mh] NOT humans[mh]). This search yielded 1488 entries. Articles were manually sorted to 194 clinical reports on patients with MMA and/or PA (any lab-based studies and case reports with less than three patients excluded) that were stratified into categories (P, F, M, B.) (Figure S1). Case reports were considered in bulk for specific questions. Eight articles published past the cut-off date and seven articles cited within the initial clinical reports were considered by the panel to be of specific importance (total of 209 articles). Articles were allocated to the categories ‘high’, ‘moderate’ and ‘low’ quality of evidence to a certain outcome by at least two panellists.

## 2.2 | Development process

In a first face-to-face meeting, panellists were informed about and received guidance on how to apply the GRADE methodology.

The panellists agreed that the guidelines should address all types of isolated MMA and PA in patients of all ages. Panellists and patient representatives selected and rated outcome parameters as critical, important, or not important using an online tool. The literature was assigned to the critical and important outcomes and discussed and evaluated in working groups (email or online/phone meetings), which formulated first drafts for recommendations. A consensus-oriented, moderated discussion of the evidence and wording of the recommendations was held during the second face-to-face meeting. Based on this meeting, the evidence profile was created, and recommendations were formulated. Since during the COVID-19 pandemic personal in-person meetings were impossible, the panellists rated the quality of the evidence for each outcome using an online tool. Final rating of the quality of evidence was based on at least 50% of votes for the category ‘high’, ‘moderate’ or ‘low’. If two categories received equal numbers of votes, the quality of the evidence was downgraded to the lower category (Figure S2A).

The strength of each recommendation was finally rated by the panellists based on the quality of the



**FIGURE 2** Scheme depicting the extra- and intracellular transport and processing of the cobalamin (Cbl) molecule and the involved proteins. Methylmalonyl-CoA mutase (MMUT), methylmalonic aciduria type A protein (MMAA), methylmalonic aciduria type B protein (MMAB), methylmalonic aciduria and homocystinuria type D protein variant 2 (MMADHC-MMA), and propionyl-CoA carboxylase (PCC) defects and their related diseases are discussed in these guidelines, hence these proteins are depicted in bold print. The other proteins are depicted using official protein nomenclature: amnionless (AMN) and cubulin (CUBN) form the cubam receptor to absorb cobalamin bound to cobalamin binding intrinsic factor (CBLIF); haptocorrin (TCN1; not shown), transcobalamin (TCN2) and transcobalamin receptor (CD320) facilitate cobalamin transport and uptake into the cell; lysosomal cobalamin transporter (ABCD4) and lysosomal cobalamin transport escort protein (LMBD1) export cobalamin from the lysosome; methylmalonic aciduria and homocystinuria type C protein (MMACHC) cleaves the R group of cobalamin (upper-axial ligand); methylmalonic aciduria and homocystinuria type D protein (MMADHC) targets cobalamin towards further processing in the cytosol or the mitochondrion; methionine synthase (MS), kept in its active form by methionine synthase reductase (MSR), uses cobalamin in its methylated form; methylmalonyl-CoA epimerase (MCEE) converts (R)-methylmalonyl-CoA to (S)-methylmalonyl-CoA; succinyl-CoA synthetase (SCS) also called succinate-CoA ligase forms succinate from succinyl-CoA in the citric acid cycle



evidence as well as the balance of benefits and harms, values, preferences and resources. Recommendations were downgraded to the lower category (weak) if the distribution of votes was exactly equal (Figure S2B).

Strong recommendations are indicated by 'we recommend'; weak recommendations by 'we suggest'. Some recommendations were considered extremely well based on clinical grounds or would have serious consequences if not followed; others were clearly supported by biochemical facts and well-established medical knowledge. In these cases, the wording of the recommendation was strengthened ('we strongly recommend'). For approval ratings for each recommendation, see Figure S3.

## 2.3 | Guidelines objective

The purpose of these guidelines is to serve health care professionals working with MMA and PA patients as an evidence-based reference to provide optimal patient care. When clear-cut recommendations could not be reached because of poor evidence quality, the presented collation of the body of the evidence may serve as a reference, when considering specific aspects of MMA and PA patient care. However, the guidelines do not replace comprehensive clinical reflection and assessment of each patient's individual situation. These guidelines attempt to provide guidance where there is sufficient evidence, while at the same time identifying knowledge gaps in the evidence.

## 3 | GUIDELINES

### 3.1 | Outcome parameters

An outcome parameter reflects a specific entity by which a patient suffering from MMA or PA can be affected. This can be a clinical sign (eg, kidney dysfunction or cardiomyopathy) or a complex mix of several factors [eg,

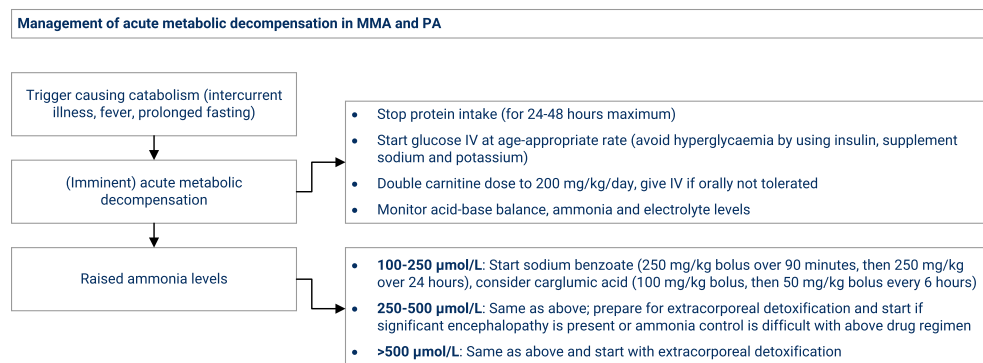
health-related quality of life (HrQoL) or metabolic stability]. Eleven outcome parameters were initially proposed by the core panellist group. After a round of open feedback from the panel and the patient representatives, four further outcomes were added. The importance of the different outcomes was gradually rated from 1 (of lowest importance) to 9 (most critical for decision-making) (Table 1). Survival was the most highly rated outcome parameter, followed by HrQoL and metabolic stability. The lowest rated outcomes were haematological abnormalities and bone health. Importantly, none of the outcomes were underestimated by the panel when compared to the patient representatives' ratings (Figure S4).

The following recommendations are structured according to a patient's natural pathway from initial presentation and diagnostic procedures to management, long-term complications and monitoring. The above-defined outcomes guide this path and each of the recommendations directly refers to an outcome.

### 3.2 | Diagnostic challenges

#### 3.2.1 | Clinical presentation

A patient can only be diagnosed with MMA or PA when the physician recognises the clinical picture suggestive of MMA or PA, which can be a challenging process as many of the clinical signs are non-specific. MMA and PA can present with acute, chronic or intermittent symptoms, which can often aggravate or even occur for the first time following a 'trigger' event. Symptoms include vomiting, weight loss, hypoglycaemia, neurological deterioration with hypotonia, irritability and lethargy eventually leading to coma in the case of an acute early onset neonatal presentation. This clinical presentation can be accompanied by the biochemical findings of metabolic acidosis, ketosis, hyperlactataemia and hyperammonaemia. Triggers of an acute episode include but are not limited to post-partum neonatal stress and other forms of catabolic



**FIGURE 3** Proposed management flowchart for MMA and PA patients during an acute metabolic decompensation, based on expert opinion. All drugs are given intravenously (IV). MMA, methylmalonic acidemia; PA, propionic acidemia

**TABLE 1** Outcome parameters and their ratings of importance

Outcome parameter	Median rating of importance of outcome
Survival	9
Health-related quality of life	9
Metabolic stability	8
Cognitive development	8
Epilepsy	8
Metabolic stroke	7
Vision and hearing	7
Early diagnosis	7
Cardiomyopathy	7
Kidney dysfunction	7
Pancreatitis	6
Normal growth	6
Neutropenia	6
Anaemia	5.5
Bone health	5

Note: Each outcome parameter was rated by the panellists and the patient representatives from 0 (lowest importance) to 9 (most critical for decision-making). The second column represents the median value of all the ratings.

states induced by infection or prolonged fasting. Late-onset patients present with a wider range of signs, involving failure to thrive, a range of neurological symptoms (encephalopathy, developmental delay), cardiac and kidney manifestations. We provide a slightly updated table of main and rare signs and symptoms occurring during acute or chronic presentation of MMA or PA (Table 2).

**Recommendation #1.** We strongly recommend considering MMA and PA in the differential diagnosis of an acute or intermittent neurological deterioration, and in the differential diagnosis of neonatal sepsis.

**Outcome:** Survival.

**Quality of evidence:** moderate.

**Strength of recommendation:** very strong (supported by medical knowledge).

### 3.2.2 | Laboratory diagnosis

When, based on clinical assessment and basic laboratory parameters or on an abnormal result from newborn screening, an organic acidemia is suspected, the diagnosis of MMA or PA is achieved by measurements of organic acids in urine (Table 3). Elevations of

methylmalonic acid together with 3-hydroxypropionate and presence of 2-methylcitrate confirm a diagnosis of MMA, while the same pattern without abnormal levels of methylmalonic acid is present in PA. Often, tiglylglycine and propionylglycine can be found in PA. The diagnostic work-up may be complemented with the measurement of acylcarnitines in dried blood spots or plasma. In this test, a striking elevation of C3 acylcarnitine (propionylcarnitine) can be found in both MMA and PA. In addition, plasma amino acid measurements show elevated glycine levels in MMA and PA.

**Recommendation #2.** We strongly recommend measurement of organic acids in urine to achieve a reliable diagnosis of MMA or PA.

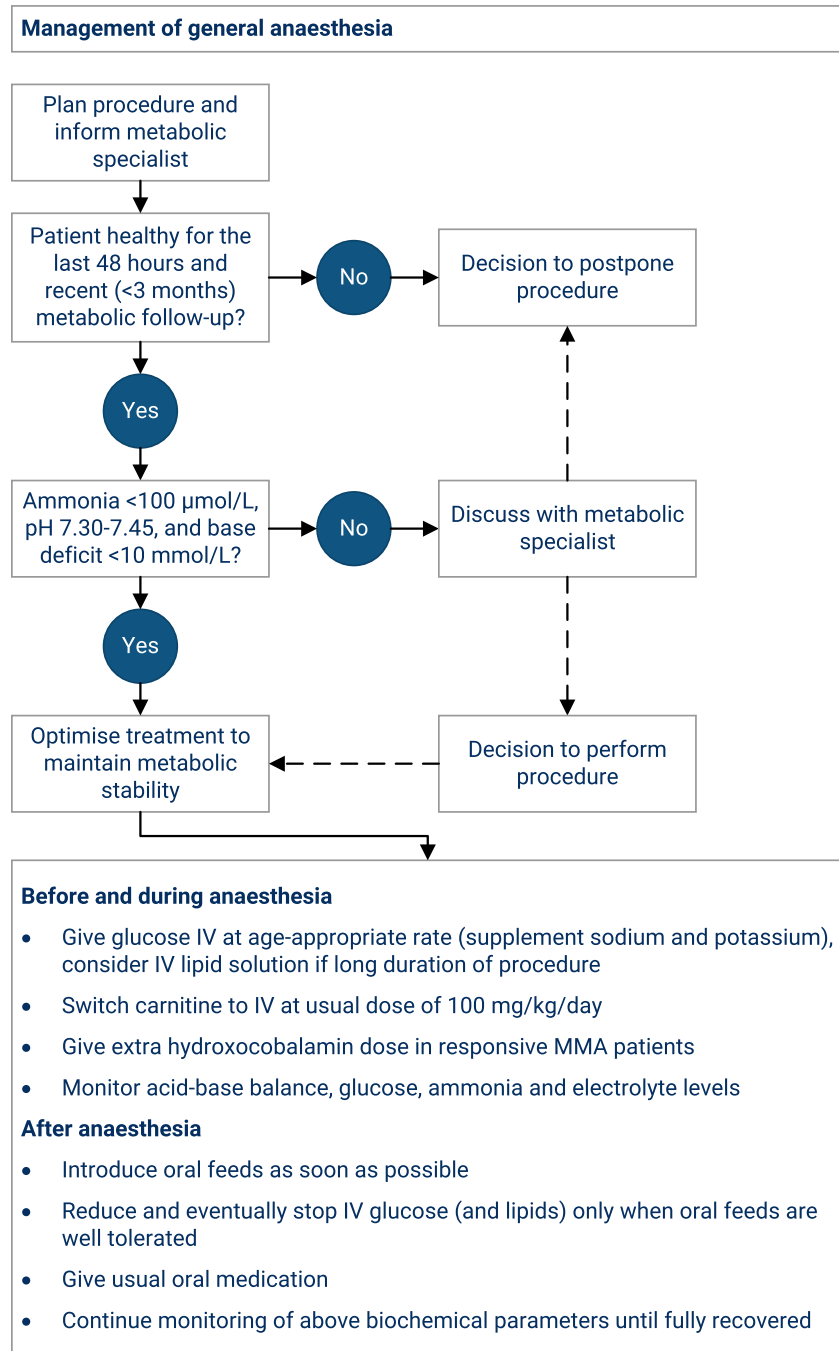
**Outcome:** Early diagnosis.

**Quality of evidence:** high.

**Strength of recommendation:** very strong (supported by biochemical knowledge).

### 3.2.3 | Differential diagnosis

As illustrated (Figure 1), the methylmalonyl-CoA mutase enzyme can be dysfunctional due to several different genetic defects, all of which lead to an elevated level of methylmalonic acid in urine and in blood. The differential diagnosis of raised methylmalonic acid entails a range of diseases. Specifically, methylmalonic acid can be raised due to a defect in *MMUT* or one of the genes distal in the intracellular cobalamin pathway, causing the MMA subtypes discussed in these guidelines, or due to defects more proximal in the intracellular cobalamin pathway as well as nutritional deficiency of cobalamin. To differentiate the diseases discussed in these guidelines from the more proximal ones and impaired cobalamin supply, homocysteine and vitamin B12 levels in blood should be measured, which are expected to be normal in isolated MMA (except in the case of incidental concomitant nutritional vitamin B12 deficiency in isolated MMA). The magnitude of methylmalonic acid elevation can further help the classification of the different defects in the pathway<sup>3</sup> (Table 3). In addition, other rare genetic defects lead to an isolated, albeit milder elevation of methylmalonic acid with normal homocysteine but are not part of these guidelines. These genes include *MCEE*, encoding methylmalonyl-CoA epimerase, and *SUCLG1*, *SUCLA2*, which encode succinate-CoA ligase, and others (Figure 2). *MCEE* deficiency can in very rare cases present with an acute metabolic decompensation, but is clearly clinically less severe compared to isolated MMA.<sup>7</sup>



**FIGURE 4** Proposed management flowchart for MMA and PA patients undergoing general anaesthesia, based on expert opinion. MMA, methylmalonic acidemia; PA, propionic acidemia

As the propionyl-CoA carboxylase enzyme requires biotin as a cofactor, nutritional biotin deficiency or a defect of the enzymes biotinidase (*BTBD* gene, OMIM #609019) or holocarboxylase synthetase (*HLCS* gene, OMIM #609018) must be excluded to finalise the diagnosis of PA. In all these cases, the urinary organic acid profiles would not only include elevated levels of the metabolites pathognomonic for PA (3-hydroxypropionate and 2-methylcitrate), but also other metabolites arising from deficiencies of other biotin dependent carboxylases such as methylcrotonylglycine.

Both MMA and PA are inherited in an autosomal recessive fashion. To confirm the biochemical diagnosis, guide management and allow genetic counselling of families, it is necessary to identify the underlying genetic defect. Isolated MMA can be caused by defects in four different genes, including *MMUT* (*mut* subtypes), *MMAA* (*cblA*), *MMAB* (*cblB*), *MMADHC* (*cblD-MMA*).<sup>3</sup> Specific mutations in *MMADHC* can also lead to a combined phenotype of MMA and homocystinuria or isolated homocystinuria.<sup>8</sup> In the rare case of inconclusive genetic results, complementation studies, the propionate



**TABLE 2** Potential signs and symptoms at presentation observed in MMA and PA patients

Acute presentation	Chronic presentation
<i>Nervous system</i>	
Acute encephalopathy	Hypotonia
Seizures	Developmental delay
Movement disorders (more frequent in PA)	Seizures
Stroke-like episodes (more frequent in MMA)	Movement disorders/dystonia
<i>Gastrointestinal system</i>	
Vomiting	Recurrent vomiting with ketoacidosis
Feeding difficulties	Failure to thrive
	Pancreatitis
<i>Haematopoietic system</i>	
Neutropenia, pancytopenia	Neutropenia, pancytopenia
<i>Heart (mostly in PA)</i>	
Acute cardiac failure (mostly based on cardiomyopathy)	Cardiomyopathy
Arrhythmias	Prolonged QTc in ECG
<i>Kidney</i>	
	Chronic renal failure (almost exclusively in MMA)

Abbreviations: ECG, electrocardiogram; MMA, methylmalonic acidemia; PA, propionic acidemia; QTc, corrected QT interval.

incorporation assay or enzyme activity measurements in fibroblasts can aid in the diagnostic process.<sup>3,9,10</sup> Many of the known *MMUT* mutations have been functionally tested with the aforementioned assays, allowing the historic classification as a *mut*<sup>0</sup> subtype (no response to hydroxocobalamin supplementation in the propionate incorporation assay) or a *mut*<sup>-</sup> subtype (increased propionate incorporation upon addition of hydroxocobalamin to the cell culture medium).<sup>11,12</sup>

In the case of PA, there is no evidence that identification of the underlying gene defect (in *PCCA* or *PCCB*) can guide management or prognosis, as no genotype-phenotype correlation is known.<sup>13</sup> However, molecular genetic confirmation of the disease is useful for genetic counselling and potential prenatal diagnosis.

**Recommendation #3.** We suggest molecular genetic testing in any patient with a biochemical diagnosis of MMA and PA for confirmation of the diagnosis, allocation to subgroups (*mut*<sup>0</sup>, *mut*<sup>-</sup>, *cblA*, *cblB*, *cblD-MMA*), genetic counselling, and to enable prenatal diagnosis.

**Outcome:** Early diagnosis.

**Quality of evidence:** moderate.

**Strength of recommendation:** weak.

### 3.2.4 | Prenatal testing

Prenatal diagnosis is preferentially performed by molecular analyses in foetal DNA. Biochemical analyses for MMA or PA can be used as an alternative or additional method in cases where the genetic results are inconclusive or not available. Prenatal diagnosis of MMA can be performed by measurement of MMA in dried amniotic fluid<sup>14</sup> and of PA by determination of 2-methylcitrate with the same method.<sup>15</sup> The combination of two independent methods (biochemical and genetics) increases the reliability of results.<sup>16</sup> These guidelines only recommend on the mode of prenatal diagnosis and do not address individual, cultural and ethical values and considerations.

**Recommendation #4.** We suggest using genetic testing for prenatal diagnosis of MMA and PA.

**Outcome:** Early diagnosis.

**Quality of evidence:** moderate.

**Strength of recommendation:** weak.

### 3.2.5 | Newborn screening

Propionylcarnitine (C3) is a disease biomarker but can display variable elevations in the context of newborn screening for MMA and PA. From a methodological perspective sensitivity and specificity for diagnosis of MMA and PA from dried blood spots, obtained during the first days of life, can be optimised by measuring C3/C2 ratio, 2-methylcitrate,<sup>17-19</sup> 3-hydroxypropionate,<sup>20</sup> C3/C0 and C16:1OH/C2<sup>21</sup> and C17,<sup>22</sup> either as part of the initial screening or as second tier testing.

In more recent studies, newborn screening has been shown to increase the chance of early diagnosis of MMA and PA patients,<sup>23,24</sup> especially in late-onset cases.<sup>25</sup> While newborn screening may decrease neonatal mortality,<sup>26</sup> it may not prevent neonatal metabolic decompensation, potentially due to the delay until the newborn screening result is available. Additionally, newborn screening may not improve important outcome parameters, including metabolic stability and cognitive development.<sup>23,27-30</sup> In countries in which MMA and PA is not part of newborn screening but the method is based on obtaining a full acylcarnitine profile, immediate 'unblinding' of the profile in children with suggestive

TABLE 3 Biochemical presentation of PA and conditions with raised methylmalonic acid

Diseases discussed in these guidelines	Organic acids in urine		Acylcarnitines in dried blood or plasma		Plasma		Vitamin B12	Holotranscobalamin
	Methylmalonic acid	3-hydroxypropionate	2-methylcitrate	Propionylcarnitine	Homocysteine			
MMA <sup>a</sup>	↑-↑↑↑	↑	↑	↑↑	n		n	n
PA	n	↑	↑(↑)	↑↑(↑)	n		n	n
<b>Other defects and deficiencies causing raised methylmalonic acid</b>								
MCEE deficiency	↑	(↑)	(↑)		n		n	n
ACSF3 deficiency <sup>b</sup>	↑	n	n	n	n		n	n
Adenosyl- and methylcobalamin synthesis defects <sup>c</sup>	↑ - ↑↑↑	↑	↑	↑-↑↑	↑ - ↑↑↑		n	n
Transcobalamin deficiency	↑	n-↑	n-↑	n-↑	↑		n-↓	↓
Transcobalamin receptor deficiency	↑	n/a	n/a	n/a	n-↑		n/a	n/a
IF deficiency and Imerslund-Najman-Gräsbeck syndrome	↑ - ↑↑	n-↑	n-↑	n-↑	↑ - ↑↑↑		↓↓	↓
Nutritional vitamin B12 deficiency	↑ - ↑↑	n-↑	n-↑	n-↑	↑ - ↑↑		↓-↓↓	↓-↓↓

Note: Pathognomonic biochemical findings for MMA and PA in urine and blood compared to other related diseases, causing raised methylmalonic acids levels. Isolated defects in the methylcobalamin pathway are not displayed.

Abbreviations: ACSF3, acyl-CoA synthetase family member 3; IF, intrinsic factor; MCEE, methylmalonyl CoA epimerase; MMA, methylmalonic acidemia; n, normal; n/a, no data available; PA, propionic acidemia.

<sup>a</sup>Subtypes *mut*, *cblA*, *cblB*, *cblD-MMA*.

<sup>b</sup>In addition to methylmalonic acid, raised malonic acid can be found in urine; biochemical parameters based on Reference 6.

<sup>c</sup>Subtypes *cblC*, *cblD-MMA/HC*, *cblF*, *cblJ*.

clinical signs and symptoms can avoid significant diagnostic delay.

A minority of countries in the European Union (7/27) performed newborn screening for MMA and PA in 2015.<sup>31</sup> As the modality of screening, including confirmatory testing, is variable, and often structured follow-up programs focussing on patient-relevant outcomes are absent, systematic evaluation of MMA and PA newborn screening programs is warranted in order to allow for a general recommendation in favour or against MMA and PA newborn screening in the future.

### 3.3 | Management of MMA and PA

#### 3.3.1 | Initial treatment

Early diagnosis and timely treatment are essential to improve survival and reduce morbidity in MMA and PA patients. Over time survival of these patients has improved.<sup>23,26,32-35</sup> Improved survival seems to be due to improved treatment strategies and patient monitoring. The effect of single treatment variables on survival, however, is not clear from the present evidence. In MMA patients, survival also depends on age of onset and disease subtype; early-onset MMA patients, in particular *mut*<sup>0</sup> and *cblB* patients, have a higher mortality risk.<sup>33,34</sup>

As soon as the diagnosis of MMA and PA is suspected, specific therapies should be initiated and the patient should be referred to a specialist centre as some of the treatments and specialist knowledge are only available there.<sup>35</sup> Intensive care treatment of patients with a metabolic decompensation can be necessary if there is a severe metabolic acidosis with or without hyperammonaemia, and hyperlactataemia. The specifics of these acute treatment modalities, including extracorporeal detoxification, have not been systematically studied yet, and the contribution of individual treatments to the improved survival over the last decades is unclear. The panel has intensively discussed the available evidence and has come up with principles based on expert opinions of how to approach treatment of an (imminent) acute metabolic decompensation in MMA and PA patients (Figure 3). It seems appropriate to advise against the primary use of sodium phenylbutyrate as ammonia scavenger in MMA and PA as it can lead to decreased glutamine levels, potentially hampering tricarboxylic acid cycle anaplerosis via 2-ketoglutarate.<sup>36</sup> More recently, carglumic acid was trialled as part of hyperammonaemia treatment strategies in MMA and PA.<sup>37-39</sup> While the medication was so far tolerated with no side effects,<sup>40</sup> further systematic studies are required to prove its efficacy.<sup>41</sup> Further, it has to be noted that extensive administration

of glucose intravenously can be associated with lactic acidosis, potentially due to the inhibited pyruvate dehydrogenase enzyme in MMA and PA.

It is not possible to make evidence-based statements on improvement of survival with liver transplantation, as the published studies focus on the survival shortly after transplantation, but long-term comparisons to non-transplanted patients are absent. This applies to liver, kidney and liver-kidney transplantations, where overall survival after surgery is around 85%.<sup>42-44</sup>

**Recommendation #5.** If the diagnosis of MMA or PA is suspected, we suggest immediate specific treatment to improve survival in MMA and PA.

**Outcome:** Survival.

**Quality of evidence:** moderate.

**Strength of recommendation:** weak.

#### 3.3.2 | Metabolic stability

The term metabolic stability is often used in the clinical context, but its meaning is seldom stated explicitly. For the purpose of these guidelines, we defined metabolic stability as the absence of hospitalisation and exacerbation of disease signs and symptoms, especially metabolic acidosis and hyperammonaemia. Per this definition metabolic stability is a complex term, as it is influenced by various factors, some of which are addressed in this chapter.

Levels of biochemical metabolites, such as methylmalonic acid, propionylcarnitine and plasma amino acids, are often used as surrogate markers for metabolic stability (refer to the 'monitoring' section for details on measurement frequencies). The present evidence, though, suggests to rely on clinical assessment, including review of medical history, and the measurement of simple biochemical parameters, such as acid-base balance (decreased pH and base excess, raised anion gap), urinary ketones and plasma ammonia in the acute setting to discriminate between a metabolically stable or a decompensating situation.<sup>45,46</sup> More recently, measurement of fibroblast growth factor 21 (FGF21) and of 2-methylcitrate showed potential to predict the development of long-term complications.<sup>47-49</sup>

Trigger events leading to metabolic decompensation include infections, causing fever and catabolism. Similarly, prolonged fasting periods are leading to catabolism and should be avoided to prevent metabolic instability.<sup>50</sup> In such situations of a mild intermittent illness, it is common practice to apply enteral emergency feeds consisting of a glucose polymer solution (occasionally with fat

emulsion) to provide adequate energy and meet raised metabolic demands. The emergency feeds should only be given during a limited time and if they are tolerated, that is, absence of vomiting and diarrhoea. In parallel, protein intake (including PFAA mixtures) is stopped or partly reduced, for example, to 50%, depending on the severity of clinical symptoms. A simplified overview of age-dependent emergency regimens based on glucose polymer solution is provided (Table 4). Similarly, general anaesthesia requires specific considerations to ensure adequate energy supply and metabolic stability (Figure 4). As vaccinations do not seem to trigger decompensation themselves, as demonstrated in urea cycle disorders,<sup>51</sup> regular vaccination protocols are indicated for MMA and PA patients. Pregnancies have been described in a few cases of MMA and PA without metabolic decompensations.<sup>52-54</sup>

Generally, it is unclear whether resting energy expenditure in MMA and PA is abnormal.<sup>55-58</sup> There is no evidence in MMA and PA, but it may be considered, that energy requirements might be lower in patients after a metabolic stroke with subsequent reduced mobility. Implementation of tube feeding can ensure adequate nutrition and energy intake in a selected group of MMA and PA patients.<sup>59,60</sup>

Further, the role of upcoming therapies, such as mRNA therapy or other gene therapy approaches, on metabolic stability and other outcome parameters will need to be defined.<sup>61-65</sup>

**Recommendation #6.** We recommend avoiding catabolic metabolism in MMA and PA patients to improve metabolic stability.

**Outcome:** Metabolic stability.

**Quality of evidence:** moderate.

**Strength of recommendation:** strong (supported by experience-based medical knowledge).

More dietary aspects are also described in the section on normal growth. In general, a diet low in natural protein aims at the reduction of precursor molecules

funnelling into the defective pathway in MMA and PA. Current practice of dietary management of MMA and PA patients aims at both metabolic stability and normal growth. It is based on adequate energy supply, avoidance of prolonged fasting and reduced intake of precursor amino acids (methionine, threonine, valine, isoleucine) through a diet restricted in natural protein, and an adequate provision of vitamins, minerals and trace minerals and essential fatty acids for age. The amount of natural protein must be assessed individually and must be based on clinical and biochemical monitoring. Breastfeeding is possible considering the total natural protein intake. However, there is insufficient data to define a detailed evidence-based dietetic strategy in MMA and PA.

**Recommendation #7.** We suggest a low natural protein diet under consideration of age-appropriate total protein requirements to improve metabolic stability.

**Outcome:** Metabolic stability.

**Quality of evidence:** low.

**Strength of recommendation:** weak.

The following specific medications are also used to facilitate metabolic stability. Levocarnitine treatment – usually at a dose of 100 mg/kg/day – is applied with the rationale of restoring depleted to normal carnitine and CoA levels in MMA and PA patients, and based on its ability to bind and eliminate propionyl-CoA molecules, which are assumed to be responsible for some of the toxic metabolite effects in MMA and PA.<sup>66</sup> At least in PA, levocarnitine might be able to improve metabolic stability and help avoiding hyperammonaemic crises.<sup>36</sup> Levocarnitine is considered a well-tolerated medication with few side effects. A recent study shows elevated plasma levels of trimethylamine N-oxide in MMA and PA patients on levocarnitine treatment. Whether this finding is related to an increased risk for cardiovascular disease in MMA and PA patients on levocarnitine medication remains yet to be determined.<sup>67</sup>

**TABLE 4** Emergency regimens

Age (years)	Glucose polymer concentration (% carbohydrate)	Fat emulsion (% fat) <sup>a</sup>	Energy (kcal per 100 mL from carbohydrates and fat)
0-1	10	3.5	71.5
1-2	15	5	105
2-9	20	5	125
>10	25	5	145

*Note:* The amount of the glucose polymer solution should be determined according to age-adequate total daily fluid intake.

<sup>a</sup>Fat emulsion can be added if expected to be well tolerated.

Metronidazole – at 10 to 20 mg/kg/day in two to three doses – has been part of the standard long-term management to reduce bacterial propionate production in the gut despite low quality of evidence for a benefit. There is no evidence demonstrating neuropathy as an intrinsic long-term complication in MMA or PA, but peripheral neuropathy has been observed in PA patients under metronidazole treatment<sup>68</sup> and metronidazole is a known cause of peripheral neuropathy.<sup>69,70</sup> Other side effects include QTc prolongation and pancreatitis; hence, metronidazole treatment should be cautiously indicated in MMA and PA patients. If metronidazole is not well tolerated, alternative antibiotics, including amoxicillin or cotrimoxazole, have been applied.

Whether carginic acid can consistently reduce the number of metabolic decompensations needs to be further studied.<sup>71</sup> It has been tried to anapleuratically support Krebs cycle function by providing citrate, which was associated with reduced number of hospitalisations in three PA patients.<sup>72</sup>

**Recommendation #8.** We suggest supplementation with levocarnitine to improve metabolic stability.

**Outcome:** Metabolic stability.

**Quality of evidence:** low.

**Strength of recommendation:** weak.

Some MMA patients clearly benefit from parenteral cobalamin treatment. Patients with *cblA* will mostly improve, and *cblB* have been described to respond in one third of the cases.<sup>73</sup> Among the *MMUT*-deficient patients, the *mut*<sup>-</sup> subgroup is more likely to show benefits from cobalamin injections<sup>33</sup> although clear evidence of cobalamin responsiveness in *mut*<sup>-</sup> patients is lacking. The ideal application route is intramuscular and hydroxocobalamin is the preferred form of the cobalamin molecule. A protocol to evaluate biochemical responsiveness has been proposed previously<sup>3</sup>: (a) The patient should be metabolically stable without recent treatment changes. (b) The patient should be off hydroxocobalamin supplementation for at least 1 month prior to assessment. (c) Collect at least three baseline urine or plasma (use the same body fluid throughout) samples on different days for measurement of methylmalonic acid. (d) Inject 1 mg hydroxocobalamin intramuscularly on three consecutive days. (e) Collect urine or plasma samples over 10 days, every other day. (f) A mean decrease of urine or plasma methylmalonic acid concentration of >50% is regarded as a significant response. A similar cofactor treatment with biotin for PA patients is not recommended, as there has been no description of responsive patients so far.

**Recommendation #9.** We recommend evaluating responsiveness for parenteral vitamin B12 in every patient with suspected MMA.

**Outcome:** Metabolic stability.

**Quality of evidence:** moderate.

**Strength of recommendation:** strong (supported by basic biochemical knowledge).

Liver transplantation in MMA or PA and combined liver-kidney as well as kidney transplantation in MMA has been performed in several patients to improve the disease outcome. Despite many transplanted patients, it is difficult to provide detailed recommendations on this topic. The lack of detailed follow-up studies and natural history data leads to incomplete evidence for many of the relevant outcome parameters. For the purpose of these guidelines, we have investigated all articles of our literature search with regards to the patients who underwent organ transplantation. We have identified nearly 300 MMA and PA patients, most of which were MMA undergoing liver transplantation followed by PA patients with the same procedure. It seems that MMA patients increasingly receive a combined liver and kidney transplant. Yap et al recently performed a similar analysis, concluding that transplantation procedures in MMA and PA patients have potential benefits as well as associated risks.<sup>74</sup> We suggest considering the management flow-chart for MMA and PA patients undergoing general anaesthesia provided in Figure 4, when performing any transplantation procedure.

After liver and/or kidney transplantation, the number of metabolic decompensations decreases and some report a shortened hospital admission length during an intermittent illness.<sup>42,54,75-103</sup> Also biochemical markers (C3, C3/C2 ratio, methylmalonic acid, 2-methylcitrate, FGF21) seem to improve after transplantation.<sup>47,49,75,98,104</sup> However, acute metabolic decompensations can still occur after transplantation in MMA and PA patients and some of these decompensations have been reported to be lethal.<sup>47,102,104-109</sup> Therefore, follow-up of any transplanted MMA or PA patient by a metabolic clinician is indicated and regular metabolic monitoring seems to be essential.<sup>110</sup> Organ transplantation of patients in acute metabolic decompensation should be avoided, as the procedure itself has the potential to cause further decompensation.<sup>111</sup>

In transplanted MMA and PA patients diet normalisation,<sup>42,84,89,90,93,94,103,104,112-115</sup> liberalisation or increased protein intake<sup>75,76,78,80,83,88,91,96-98,100,102,116-118</sup> or continuation of dietary restrictions<sup>85,87,119</sup> were all applied following transplantation. Liberalised and continuous diet both led to metabolically stable situations



without acute decompensation.<sup>89,103</sup> Other patients were described to have metabolic acidosis post-transplant while being on a continued protein restriction.<sup>86,102</sup> Further research is necessary to determine if continuation of dietary restriction is necessary after transplantation. Until the evidence is clearer further care by a metabolic specialist, including biochemical monitoring and regular dietetic review, as well as continuation of levocarnitine seems appropriate.

It is of note, that the guideline panel did not include transplantation surgeons and thus the available evidence was read from the perspective of metabolic physicians. The panel suggests considering patients for liver (MMA and PA) or combined liver-kidney (MMA) transplantation who suffer from frequent metabolic decompensations, as the strongest effect of transplantations is the improvement of metabolic stability.

**Recommendation #10.** We suggest considering liver transplantation in MMA and PA, and combined liver kidney transplantation in MMA to improve metabolic stability.

**Outcome:** Metabolic stability.

**Quality of evidence:** low.

**Strength of recommendation:** weak.

### 3.4 | Long-term complications of MMA and PA

With improved survival, long-term complications become more apparent, including so far unknown affections, such as liver neoplasms, namely hepatoblastoma and hepatocellular carcinoma.<sup>120</sup> It is essential to acknowledge that despite improved survival, metabolic decompensations are still a major mortality cause,<sup>34</sup> and sudden death may occur due to prolonged QT syndrome or cardiomyopathy.<sup>13,121,122</sup> Detailed recommendations are provided according to specific outcome parameters below.

#### 3.4.1 | Neurological complications

A variety of neurological problems are associated with MMA and PA disease. Due to their complexity, they are split in separate sections according to the outcome parameters cognitive development, metabolic stroke, epilepsy, and vision and hearing impairment.

While some patient show stabilisation and even improvement of neurological symptoms following organ

transplantation,<sup>80,88,98,99,117</sup> it is essential to acknowledge that after transplantation patients are still at risk of developing neurological complications. Cognitive development often remains stable or improves post liver and liver-kidney transplantation for MMA, and liver transplantation for PA,<sup>44,80,81,86,87,92,97,104,105,115,123,124</sup> but in one PA patient cognitive abilities got worse post liver transplantation.<sup>86</sup> In both diseases, however, the available evidence mostly lacks structured assessments of neurodevelopmental outcome. Several (including severe) new neurological sequelae occurred after liver, liver-kidney and kidney transplantation in MMA and liver transplantation in PA in up to 25% of patients. These included onset of seizures, metabolic stroke,<sup>42,113</sup> Leigh syndrome,<sup>44</sup> worsening of vision and focal leukoencephalopathy,<sup>125</sup> generalised motor neuropathy<sup>85</sup> and general neurological deterioration<sup>116</sup> in MMA patients; and metabolic stroke,<sup>86,104</sup> epilepsy<sup>86</sup> and temporal mesial sclerosis<sup>126</sup> in PA patients.

#### *Cognitive development and psychiatric complications*

Lack of natural history studies in terms of domain-specific outcomes and longitudinal developmental trajectories, different time points of evaluation, variety of patient populations, use of non-standardised, variable test batteries and cut-off values for normal development are among the limitations to evaluate long-term cognitive and psychiatric outcome of MMA and PA.

In MMA cobalamin non-responsiveness, early-onset of disease, presence of hyperammonaemia or seizures at onset and a *mut<sup>0</sup>* subtype are associated with more severe cognitive involvement, while all patients show selective deficits in processing speed.<sup>33,127</sup> In addition, up to 20% of MMA patients are affected by neuropsychiatric problems.<sup>128,129</sup> Other evidence illustrates the negative impact of the number of metabolic decompensations on cognitive outcome, indicating that improvement of metabolic stability might ameliorate cognitive problems.<sup>130</sup>

On the other hand, PA seems to be generally associated with cognitive impairment, which in most studies exceeds 50% of the evaluated patient population.<sup>28,32,131-133</sup> In addition, autism spectrum disorder, anxiety and acute psychotic episodes are described.<sup>134-139</sup> The present evidence suggests, that early intervention and treatment has little effect on the cognitive outcome in PA.<sup>23</sup>

**Recommendation #11.** We suggest age-appropriate, standardised developmental, cognitive and behavioural testing, since developmental delay, intellectual disability and/or behavioural abnormalities are known complications in MMA and PA.

**Outcome:** Cognitive development.

**Quality of evidence:** moderate.

**Strength of recommendation:** weak.

### *Metabolic stroke*

The term metabolic stroke refers to the acute onset of a central neurological deficit, often associated with a decompensation of the underlying inborn error of metabolism, that cannot be accounted for by hypoxaemia or vascular insufficiency.<sup>140</sup> Metabolic strokes, particularly involving the basal ganglia area, were reported in both MMA and PA patients.<sup>28,126,141-145</sup> They often occur during an episode of metabolic decompensation or shortly thereafter. In PA, several cases with metabolic stroke without metabolic decompensation have been published.<sup>143,146-150</sup> Magnetic resonance imaging (MRI) can be of help to diagnose a metabolic stroke and should be performed based on clinical presentation and assessment.<sup>151-153</sup> One study precisely characterised globus pallidus infarcts and developed a grading method to systematically assess the volume of the lesion.<sup>154</sup> Movement disorders are common in MMA and PA and may arise as a consequence of a metabolic stroke event.<sup>33,131,155</sup>

There is no evidence for a specific management of metabolic stroke. Therefore, standard symptomatic treatment strategies for stroke in addition to the management of the acute metabolic decompensation should apply. As described above regarding the outcome of metabolic stability, liver transplantation can improve metabolic stability and often leads to the absence of metabolic decompensations,<sup>101</sup> but is unable to prevent metabolic strokes.<sup>113</sup> In some patients, brain MRI findings improved after transplantation<sup>87</sup> while also new MRI abnormalities without a clear metabolic stroke have been reported after transplantation.<sup>102</sup>

**Recommendation #12.** We strongly recommend standard appropriate investigation for metabolic stroke, if MMA or PA patients present with symptoms suspicious of a stroke-like episode.

**Outcome:** Metabolic stroke.

**Quality of evidence:** high.

**Strength of recommendation:** very strong.

### *Epilepsy*

Epilepsy is a common complication in MMA (prevalence of 23%-43% reported)<sup>33,155</sup> and PA (prevalence of 25%-59% reported).<sup>133,143,145,156,157</sup> Seizures have even been reported as the presenting symptom of the disease prior to diagnosis in several cases of PA.<sup>143,146,148</sup>

There is no sufficient evidence to recommend a specific frequency of electroencephalogram recordings in the absence of clinical symptoms of seizures. There is no

evidence to change standard epilepsy procedures and treatment regimens in MMA and PA patients. Namely, electroencephalogram evaluation should be performed in the presence of any focal neurological symptoms or clinically suspected seizures, and treatment with antiepileptic drugs should be initiated accordingly. Caution is warranted when valproic acid is used, as it can decrease the concentration of levocarnitine by excretion of valproylcarnitine.<sup>158</sup>

**Recommendation #13.** We strongly recommend monitoring symptoms of epilepsy in MMA and PA patients as seizures are a common complication in MMA and PA.

**Outcome:** Epilepsy.

**Quality of evidence:** moderate.

**Strength of recommendation:** very strong.

### *Vision and hearing*

Optic neuropathy is one of the neurological long-term complications of both MMA<sup>159-162</sup> and PA<sup>13,28,159,163,164</sup> occurring in infancy or later during the disease course, affecting about 25% of patients. Onset of optic neuropathy can be insidious and subclinical or acute.<sup>165,166</sup>

Sensorineural hearing loss seems to be less common but was reported in several cases of MMA and PA patients.<sup>23,28,122,162,163</sup>

Currently, there are no biomarkers or clinical signs which would allow a prediction as to which patients will develop visual or hearing impairment. Despite some interesting pathophysiological considerations, which mainly involve mitochondrial dysfunction,<sup>122</sup> or interference with potassium channels in the case of sensorineural deafness,<sup>167</sup> no specific treatment can be recommended for these complications.

**Recommendation #14.** We suggest monitoring of visual and hearing function, since optic neuropathy and sensorineural hearing loss are known complications in MMA and PA.

**Outcome:** Vision and hearing.

**Quality of evidence:** moderate.

**Strength of recommendation:** weak.

## 3.4.2 | Kidney dysfunction

Impaired kidney function is a well-documented long-term complication in MMA and less frequent in PA.<sup>32,34,122,156,162,168-172</sup> Occurrence of kidney dysfunction is related to the molecular subtype: *mut*<sup>0</sup> patients are

affected earlier in life than *cblB* patients; *cblA* and *mut<sup>-</sup>* patients seem to be affected even later in life.<sup>32,33,122,173</sup> Despite these differences it is thought that all patients with isolated MMA are at risk of developing renal insufficiency in their long-term course of the disease.<sup>174</sup> Although kidney disease in PA is only reported in single cases, it can be severe, even requiring transplantation of the dysfunctional organ.<sup>169</sup>

While the exact pathomechanisms remain unresolved, two pathological correlates in kidneys of MMA patients have been described as tubulo-interstitial nephritis and renal tubular acidosis.<sup>175-179</sup> Mitochondrial impairment seems to play a key role in the pathomechanisms.<sup>122,180,181</sup>

Kidney growth is predicted by height and correlates negatively with serum cystatin C and serum methylmalonic acid concentrations.<sup>182</sup> Estimation of glomerular filtration rate (GFR) is more accurate using cystatin C instead of the traditional creatinine, as it is independent of muscle mass.<sup>4,182</sup> As measuring GFR is a complex procedure and often not available, we suggest using cystatin C based estimated GFR. Regular blood pressure monitoring should be part of kidney function assessments. While FGF21 levels do not seem to correlate with kidney function,<sup>48</sup> plasma lipocalin-2 can be used as a biomarker.<sup>172,180</sup>

There is no evidence allowing recommendations of specific treatment strategies for kidney impairment or failure in MMA and PA patients, hence, we suggest following standard protocols.

**Recommendation #15.** We strongly recommend monitoring of kidney function, as chronic kidney disease is a complication in MMA and PA.

**Outcome:** Renal dysfunction.

**Quality of evidence:** high.

**Strength of recommendation:** very strong.

In MMA, combined liver and kidney transplantation seems to be an efficient treatment of kidney failure, resulting in good renal function, even up to 10 years after transplantation.<sup>95,117,118,183,184</sup> Kidney transplant improves renal function shortly after transplantation and in some even for years (1.5 years up to 14 years) after transplantation,<sup>54,85,88,179</sup> but recurrence of nephropathy and renal failure has also been reported after kidney transplant.<sup>47,185</sup> After liver transplantation several patients showed normal renal function even up to 15 years after transplantation,<sup>119,184</sup> while others have or develop (progressive) renal failure after transplantation.<sup>94,101,106,116,119</sup> Liver transplantation seems not to correct an already dysfunctional kidney.<sup>97</sup>

In PA, one patient was reported with kidney transplant 17 years after liver transplant.<sup>91</sup>

In the context of transplantation, it has to be considered that calcineurin inhibitors can be nephrotoxic, which was also found in MMA<sup>96,186</sup> and PA patients.<sup>86</sup>

### 3.4.3 | Cardiac disease

Cardiomyopathy occurs in few MMA and in approximately 25% of PA patients.<sup>28,34,84,145,162,170,187,188</sup> Cardiomyopathy can present as an isolated clinical finding in previously asymptomatic individuals.<sup>189,190</sup> There does not seem to be a correlation between the occurrence of cardiomyopathy and metabolic stability, severity of the phenotype or residual enzymatic activity.<sup>84</sup> Cardiomyopathy can be rapidly progressive leading to cardiac failure or even death.<sup>48</sup>

Long QT syndrome was reported in 22% and 33% of PA patients in two large cohorts.<sup>28,162</sup> Others observed an even higher incidence of prolonged QTc interval (70%) and arrhythmias (20%) in 10 PA patients with.<sup>191</sup> Prolonged QTc and ventricular arrhythmias can result in sudden cardiac arrest in PA patients.<sup>191,192</sup>

There is weak evidence that high doses of coenzyme Q10 can improve cardiac function in PA patients with cardiomyopathy.<sup>193</sup> Beyond that, there is not enough evidence to recommend any specific management of cardiomyopathy or long QT syndrome in MMA and PA beyond standard cardiac therapy.

Based on the above-described cardiac complications, we suggest using electrocardiogram and echocardiogram for regular monitoring (Table 5)

**Recommendation #16.** We strongly recommend regular cardiac examinations, since cardiomyopathy in MMA and PA and long QT syndrome in PA are potentially life-threatening complications.

**Outcome:** Cardiac disease.

**Quality of evidence:** high.

**Strength of recommendation:** very strong.

There are several reports showing stabilisation or improvement of cardiomyopathy after liver transplantation.<sup>84,89,91,98,102,114,184,185,194</sup> However, these results are counterbalanced by studies illustrating the development of cardiomyopathy and prolonged QTc after transplantation and reporting patients to have died as a consequence of heart failure.<sup>91,105,188,195</sup> Cardiac complications may at least partly be attributed to medication and/or immunosuppressants used in the context of post-transplant treatment, hence more systematic data of cardiac parameters

**TABLE 5** Monitoring

Assessment	Frequency
<i>Metabolic follow-up</i>	
Plasma: NH <sub>3</sub> , acid base balance (via blood gas analysis <sup>a</sup> ), lactate; urine: ketones	Each clinic visit
Quantitative plasma amino acids (3-4 h of fasting prior to sample collection)	3-6 monthly
Methylmalonic acid in plasma (and urine if available)	3-6 monthly
Acylcarnitine profile in dried blood or plasma (propionylcarnitine and free carnitine)	3-6 monthly
<i>Diet and nutritional status</i>	
Diet history	Each clinic visit
Growth (weight, length or height, head circumference)	Each clinic visit <sup>b</sup>
Full clinical examination	Each clinic visit
Albumin, total protein, transferrin	6-monthly
Bone health (Ca, P, ALP, Mg, PTH, 25-OH vitamin D in blood; Ca, P in urine) <sup>c</sup>	12-monthly
Full blood count, iron status, folic acid, vitamin B12	12-monthly
<i>Long-term complications</i>	
Neurological examination with assessment of developmental milestones	Each clinic visit
Kidney function (blood pressure, serum creatinine, electrolytes, cystatin C, uric acid; urinary electrolytes and protein loss; GFR) <sup>c,d</sup>	6-monthly
Pancreas function (lipase, pancreatic amylase)	6-monthly
Cardiac assessment (ECG)	12-monthly
Formal developmental/cognitive assessment	When clinically indicated
EEG, cerebral MRI	When clinically indicated
Ophthalmologic assessment	12-monthly
Formal hearing test	When clinically indicated

Abbreviations: ALP, alkaline phosphatase; Ca, calcium; ECG, electrocardiogram; EEG, electroencephalogram; GFR, glomerular filtration rate; Mg, magnesium; MRI, magnetic resonance imaging; P, phosphate; PA, propionic acidemia; PTH, parathyroid hormone.

<sup>a</sup>Venous or capillary blood sample.

<sup>ab</sup>More frequently in infants.

<sup>c</sup>More frequently in the presence of chronic kidney disease.

<sup>d</sup>GFR: if available 12-monthly, alternatively use estimated GFR based on cystatin C; in PA 12-monthly biochemistry is sufficient.

and used medication must be collected to enable specific recommendations regarding organ transplantation in the context of cardiac outcome in MMA and PA. Potentially,

heart transplantation can be an option for PA patients with isolated cardiomyopathy.<sup>196</sup>

### 3.4.4 | Haematological complications

Haematological abnormalities are common in MMA and PA.<sup>122,162</sup> Pancytopenia (especially neutropenia) at initial presentation or during metabolic decompensation as well as during the chronic disease course has been frequently described.<sup>13,23,28,148,197-200</sup> Isolated thrombocytopenia can be observed during acute metabolic decompensations.<sup>13,23,28,148</sup> Anaemia may rather present chronically and depend on other factors such as the presence of chronic kidney disease. Other postulated mechanisms include reversible suppressive effects of toxic metabolites on bone marrow function.<sup>198,201</sup>

Deficiencies of substrates for blood cell production (vitamin B12, folic acid, iron) should be excluded in patients with haematological abnormalities. Treatment of anaemia with erythropoietin in patients with chronic kidney disease should follow common nephrology standards. Indication for treatment with granulocyte colony stimulating factor is unclear, as there is very limited experience in MMA and PA patients.<sup>13</sup>

**Recommendation #17.** We suggest monitoring of full blood count during regular follow-up and in case of metabolic decompensation, since anaemia, neutropenia and/or thrombocytopenia can be a complication in MMA and PA patients.

**Outcome:** Haematological complications.

**Quality of evidence:** moderate.

**Strength of recommendation:** weak.

### 3.4.5 | Bone health

Patients with MMA and PA are at risk of low bone density and osteoporosis,<sup>128,202,203</sup> which may be aggravated by kidney dysfunction in MMA. Risk factors for low bone density and osteoporosis in MMA and PA patients can include chronic acidosis (causing osteoclast activation and osteoblast inhibition), impaired kidney function and inadequate dietary intake of calcium, phosphate and vitamin D. Further it has been hypothesised, that the application of amino acid supplements can decrease bone mineralisation, as it increases the load of extracted acids, leading to buffering of protons in the bone tissue and increased bone resorption.<sup>122</sup> Optimisation of calcium and phosphate intake and vitamin D supplementation might be beneficial for bone health.



The time and frequency of assessment of bone health in MMA and PA should be guided by the risk of the individual patient. If bone density measurements (dual-energy X-ray absorptiometry [DEXA] scans) are applied in growing children and adolescents, they should be combined with assessment of bone age (and pubertal status) for adequate interpretation of the results. Osteoporosis can only be diagnosed in the presence of clinically significant fracture history, which has only been scarcely observed in MMA and PA.<sup>204</sup> In patients with renal failure, the diagnosis of osteoporosis should only be made in the absence of renal osteodystrophy.

For osteopenia or osteoporosis, treatment decisions need to be individualised, integrating parameters of bone metabolism, including secondary hyperparathyroidism in patients with chronic renal failure. Once the diagnosis of osteoporosis is established, treatment should follow common recommendations. Antiresorptive drugs (eg, bisphosphonates) may be indicated in patients at increased risk for fractures with relevant bone loss documented in serial DEXA measurements despite optimisation of nutritional support. The role of antiresorptive drugs for treatment or prevention of osteoporosis has not been systematically studied in MMA and PA patients.

**Recommendation #18.** We suggest assessment of bone health, considering the risk of patients with MMA and PA for impaired bone health.

**Outcome:** Bone health.

**Quality of evidence:** low.

**Strength of recommendation:** weak.

### 3.4.6 | Growth

Poor growth outcomes (weight, linear growth and head circumference) are observed in MMA and PA patients<sup>122,162,170,173,205,206</sup> with a higher prevalence in MMA.<sup>122</sup> Lower birthweights compared to the normal reference population are seen in newborns with MMA but not in PA.<sup>207</sup>

Poor growth is more pronounced in *mut*<sup>0</sup> and *cblB* subtypes than *cblA* and *mut*<sup>-</sup> subtypes<sup>33,58,206</sup> with no reported difference between early and late-onset patients.<sup>207</sup> Linear growth appears more affected than weight gain which can result in overweight and obesity in MMA and PA patients.<sup>28,58,59,122,208</sup> A high percentage of fat mass is reported in MMA, particularly in *mut*<sup>0</sup> and *cblB*,<sup>205,58</sup> and PA patients.<sup>208</sup> Failure to thrive was associated with intellectual disability and increased mortality in cobalamin non-responsive MMA patients.<sup>194</sup> In MMA,

body length SD score decreased over time in patients with movement disorders compared to those without.<sup>162</sup> Linear growth improves in liver transplanted patients with MMA, when protein intake was relaxed but not unrestricted.<sup>101</sup>

The causes for poor growth are considered to be multifactorial. Nutritional reasons are commonly cited and include over-restriction of natural protein,<sup>209-211</sup> inadequate protein and energy intakes,<sup>212</sup> use of PFAAs,<sup>203,206,208,213,214</sup> malnutrition secondary to feeding difficulties<sup>206</sup> and frequent hospitalisations for metabolic decompensations preventing the usual diet and nutrients intake.<sup>215</sup> While total energy intake does not seem to correlate with linear growth a protein to energy ratio of 1.5 to 2.9 g protein/100 kcal/day is positively correlated with growth outcomes in patients with inborn errors of intermediary protein metabolism.<sup>208</sup>

Use of PFAAs is common practice in some centres with a variable prescription regarding percentage of total protein intake.<sup>33,60,203,209-211,215</sup> However, PFAAs are low in valine and isoleucine but high in leucine content and can result in low plasma isoleucine and valine levels and iatrogenic amino acid deficiencies associated with adverse growth outcomes.<sup>206</sup> The height z-score seems positively correlated with natural-protein-to-energy prescription ratio and plasma L-valine and L-arginine levels, while negatively associated with the amount of PFAAs.<sup>214</sup> Hence, PFAAs should not substitute for an adequate provision of natural protein and the need for PFAAs requires further review.<sup>206,208</sup> It is common practice to monitor plasma amino acids on a regular basis and adjust the dietary regimen accordingly.

**Recommendation #19.** We suggest regular monitoring of anthropometric measurements in MMA and PA patients, as growth outcomes can be poor.

**Outcome:** Normal growth.

**Quality of evidence:** moderate.

**Strength of recommendation:** weak.

Growth can potentially be improved after organ transplantation, but persistent growth delay and even decreased growth rate have also been reported.<sup>44,80,81,97,100,102,104,106,118,216</sup> Factors influencing growth after transplantation need to be determined.

### 3.4.7 | Pancreatitis

Acute, recurrent acute and chronic pancreatitis are possible long-term complications of MMA<sup>32,122,217</sup> and



PA.<sup>13,23,28,122,205,218,219</sup> Pancreatitis has been observed in around 5% to 10% of patients<sup>13,122,205</sup> and may develop independently from metabolic decompensations and metabolic control.<sup>13,194</sup> There is weak evidence that pancreatitis correlates with mortality.<sup>32,194</sup>

Like in individuals without MMA or PA, the clinical presentation of pancreatitis is variable. It is of note that pancreatitis can occur without abdominal pain and may therefore be under-recognised.<sup>220,221</sup>

There is no evidence that management of acute or chronic pancreatitis in MMA and PA has specific aspects different from general standards on pancreatitis treatment. Adequate energy supply should be maintained throughout an episode of pancreatitis to ensure metabolic stability.

**Recommendation #20.** We strongly recommend prompt evaluation for pancreatitis in MMA and PA patients if clinically suspected, since both acute and chronic pancreatitis are known complications in PA and MMA.

**Outcome:** Pancreatitis.

**Quality of evidence:** moderate.

**Strength of recommendation:** very strong.

### 3.5 | Health-related quality of life

HrQoL and psychological adjustment are meaningful outcome parameters that should be considered in the care for children with chronic disease.<sup>222,223</sup> The high rating of the outcome HrQoL illustrates the importance of this parameter to health professionals and experts as well as patient representatives. In MMA and PA, HrQoL has so far scarcely been systematically addressed.<sup>224</sup> Most of our knowledge on HrQoL in MMA and PA has been extrapolated from studies in combined samples of inherited metabolic disease patients applying generic or chronic generic instruments. Only very few reports present isolated data on HrQoL in PA or MMA patients.

HrQoL was addressed in 13 PA patients, using a generic instrument (KINDL), and found significantly lower HrQoL for the 'psychological' and 'friends' domain. Higher HrQoL was reported for the 'school' domain. Correlations with disease- or family-related parameters or impact of interventions on HrQoL were not investigated.<sup>28</sup>

For 35 MMA *mut<sup>0</sup>* patients their parents or caregivers completed the PedsQI generic core, transplant as well as family impact modules proxy versions. They reported lower mean PedsQI core scale scores (in comparison to healthy children) and lower scores on the

transplant scales (as compared to other indication groups for liver transplantation). Compared to families of children with other complex chronic conditions, MMA families had a lower quality of life. Free comments suggested a favourable effect of liver transplantation on HrQoL.<sup>225</sup>

Recently, Zeltner et al have developed a specific questionnaire for the assessment of HrQoL in intoxication-type metabolic disorders.<sup>226</sup> In contrast to generic instruments, specific tools are tailor-made for disease groups with patients participating in the process.<sup>227</sup> Specific instruments are more suitable to detect changes over time or following interventions.

If considered, we strongly recommend systematic assessment of HrQoL with standardised instruments. We recommend choosing generic, chronic generic and/or specific instruments in line with the question to be addressed. While there is weak evidence suggesting that MMA and PA patients and their families have impaired HrQoL, there is not enough evidence to give recommendations on interventions to improve HrQoL in MMA and PA.

**Recommendation #21.** We recommend considering health-related quality of life a relevant outcome parameter in MMA and PA.

**Outcome:** Health-related quality of life.

**Quality of evidence:** moderate.

**Strength of recommendation:** strong.

### 3.6 | Monitoring

There is no strong evidence base as to when which monitoring investigations are indicated in MMA and PA patients. The panel recommends a slightly modified monitoring scheme compared to the initial guidelines (Table 5), which can guide clinical management but should be tailored to individual patients' needs. In addition to the items represented in the table, we recommend regular contact to a metabolic dietitian. A full clinical examination should be performed at each patient visit, focusing on the cardiovascular system and neurological aspects but also comprising an assessment of skin, nails and hair as part of the nutritional assessment of the patient.

## 4 | CONCLUDING REMARKS

This update of the MMA and PA guidelines provides a digest of evaluated clinically relevant evidence published

on these disorders. Based on the present evidence, 21 recommendations were formulated by a diverse panel of metabolic disease health care professionals. It has to be noted, though, that the participants predominantly had a European/Mediterranean background. For a next revision, it is intended to overcome this limitation and form a more heterogeneous panel. There remain significant knowledge gaps regarding the optimal management of MMA and PA patients. While more and better-quality evidence is needed in the study of MMA and PA, we will continue to evaluate the literature on a regular basis to enable health care professionals working in the field to make well-informed decisions, which are not based on dogmatic expert knowledge.

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## CONFLICT OF INTEREST

D. B. participated in European Metabolic Group meetings sponsored by Nutricia and received research funds from Nutricia. S. C. G. has received a research fund from Nutricia as well as reimbursement for attending a symposium by MetaX and Vitaflo and fees for speaking on educational events from Nutricia and Vitaflo. J. O. S.

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## AUTHOR CONTRIBUTIONS

All authors were involved in the conception of the paper and the evaluation of literature as well as development of recommendations. Patrick Forny, Friederike Hörster, Martina Huemer and Matthias R. Baumgartner coordinated the panel. Patrick Forny is the guarantor of the paper.

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## SUPPORTING INFORMATION

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